

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
21 July 2005 (21.07.2005)

PCT

(10) International Publication Number
WO 2005/066178 A1

(51) International Patent Classification⁷: **C07D 487/16**, A61K 31/505, A61P 25/00

(74) Agents: ASAMURA, Kiyoshi et al.; Room 331, New Ohtemachi Bldg., 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo, 1000004 (JP).

(21) International Application Number:

PCT/JP2005/000323

(22) International Filing Date: 6 January 2005 (06.01.2005)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

2004-001312 6 January 2004 (06.01.2004) JP

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): TAISHO PHARMACEUTICAL CO., LTD. [JP/JP]; 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP).

(72) Inventors; and

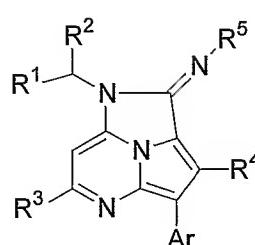
(75) Inventors/Applicants (for US only): NAKAZATO, Atsuro [JP/JP]; c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP). OKUBO, Taketoshi [JP/JP]; c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP). NOZAWA, Dai [JP/JP]; c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP). TAMITA, Tomoko [JP/JP]; c/o Taisho Pharmaceutical Co., Ltd., 24-1, Takada 3-chome, Toshima-ku, Tokyo, 1708633 (JP). KENNIS, Ludo, E.J. [BE/BE]; c/o Janssen Pharmaceutica N.V., Turnhoutseweg 30, Beerse, B-2340 (BE).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TRIAZA-CYCLOPENTA[CD]INDENE DERIVATIVES



[I]

(57) Abstract: An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastritis, drug dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, dermatitides, schizophrenia, pain, etc. A triaza-cyclopenta[cd]indene derivative represented by the following formula [I]: has a high affinity for CRF receptors and is effective against diseases in which CRF is considered to be involved.

DESCRIPTION

TRIAZA-CYCLOPENTA[cd]INDENE DERIVATIVES

DETAILED DESCRIPTION OF THE INVENTION

TECHNICAL FIELD

The present invention relates to a therapeutic agent for diseases in which corticotropin releasing factor (CRF) is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc.

10 DESCRIPTION OF THE PRIOR ART

CRF is a hormone comprising 41 amino acids (Science, 213, 1394-1397, 1981; and J. Neurosci., 7, 88-100, 1987), and it is suggested that CRF plays a core role in biological reactions against stresses (Cell. Mol. Neurobiol., 14, 579-588, 1994; Endocrinol., 132, 723-728, 1994; and Neuroendocrinol. 61, 445-452, 1995).
15 For CRF, there are the following two paths: a path by which CRF acts on peripheral immune system or sympathetic nervous system through hypothalamus-pituitary-adrenal system, and a path by which CRF functions as a neurotransmitter in central nervous system (in Corticotropin Releasing Factor: Basic and Clinical Studies of a Neuropeptide, pp. 29-52, 1990). Intraventricular administration of CRF to hypophysectomized rats and normal rats causes an anxiety-like symptom in both types of rats (Pharmacol. Rev., 43, 425-473, 1991; and Brain Res. Rev., 15, 71-100, 1990). That is, there are suggested the participation of CRF in hypothalamus-pituitary-adrenal system and the pathway by which CRF functions as a neurotransmitter in central nervous system.
20
25

The review by Owens and Nemeroff in 1991 summarizes diseases in which CRF is involved (Pharmacol. Rev., 43, 425-474, 1991). That is, CRF is involved in depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea,

eating disorder, hypertension, gastrointestinal diseases, drug dependence, inflammation, immunity-related diseases, etc. It has recently been reported that CRF is involved also in epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, and cephalic external wound (Brain Res. 545, 339-342, 1991; Ann. Neurol. 5 31, 48-498, 1992; Dev. Brain Res. 91, 245-251, 1996; and Brain Res. 744, 166-170, 1997). Accordingly, antagonists against CRF receptors are useful as therapeutic agents for the diseases described above.

PROBLEM(S) TO BE SOLVED BY INVENTION

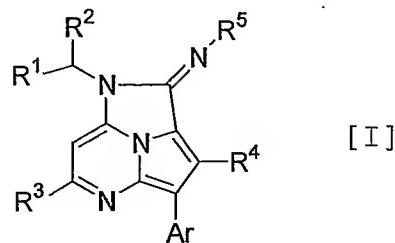
An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc.

MEANS FOR SOLVING PROBLEM

The present inventors earnestly investigated triaza-cyclopenta[cd]indene derivatives that have a high affinity for CRF receptors, whereby the present 20 invention has been accomplished.

The present invention is triaza-cyclopenta[cd]indene derivatives explained below.

A triaza-cyclopenta[cd]indene derivative represented by the following formula [I]:



25 (wherein R¹ and R² are the same or different, and independently are hydrogen, C₁-

3

C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl- C_{1-6} alkyl, C_{1-6} alkoxy- C_{1-6} alkyl, hydroxy- C_{1-6} alkyl, cyano- C_{1-6} alkyl, carbamoyl- C_{1-6} alkyl or di(C_{1-6} alkyl)amino- C_{1-6} alkyl, cyano, carbamoyl or aryl;

R^3 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl- C_{1-6} alkyl, halogen, 5 C_{1-6} alkoxy, C_{3-7} cycloalkyloxy, C_{1-6} alkylthio or $-\text{N}(\text{R}^6)\text{R}^7$;

R^4 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl- C_{1-6} alkyl;

R^5 is hydrogen, C_{1-6} alkyl, aryl- C_{1-6} alkyl or carbamoyl;

Ar is aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected 10 from the group consisting of halogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, cyano, nitro, hydroxy, $-\text{CO}_2\text{R}^8$, $-\text{C}(=\text{O})\text{R}^9$, $-\text{CONR}^{10}\text{R}^{11}$, $-\text{OC}(=\text{O})\text{R}^{12}$, $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$, - $\text{S}(=\text{O})_r\text{NR}^{15}\text{R}^{16}$, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy and $-\text{N}(\text{R}^{17})\text{R}^{18}$;

15 R^8 and R^{14} are the same or different, and independently are hydrogen or C_{1-5} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-5} alkyl, aryl or aryl- C_{1-5} alkyl;

R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{15} , R^{16} , R^{17} and R^{18} are the same or different, and independently are hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl;

r is 1 or 2) or individual isomers thereof or racemic or non-racemic

20 mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

The terms used in the present specification have the following meanings.

The term " C_{1-6} alkyl" means a straight chain or branched chain alkyl group of 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, *sec*-butyl, pentyl, isopentyl, hexyl, isohexyl or the like. 25

The term " C_{3-7} cycloalkyl" means a cyclic alkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or the like.

The term " C_{3-7} cycloalkyl- C_{1-6} alkyl" means a substituted C_{1-6} alkyl group 30 having the above-mentioned C_{3-7} cycloalkyl as the substituent, such as cyclopropylmethyl, 2-cyclopropylethyl, 2-cyclopentylethyl or the like.

The term " C_{1-6} alkoxy" means a straight chain or branched chain alkoxy group of 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy,

butoxy, isobutyloxy, pentyloxy, isopentyloxy or the like.

The term "C₃₋₇cycloalkyloxy" means a cyclic alkoxy group of 3 to 7 carbon atoms, such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy or the like.

The term "C₁₋₆alkoxy-C₁₋₆alkyl" means a substituted C₁₋₆alkyl group having 5 the above-mentioned C₁₋₆alkoxy group as the substituent, such as methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl or the like.

The term "hydroxy-C₁₋₆alkyl" means a substituted C₁₋₆alkyl group having 10 hydroxy group, such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 4-hydroxybutyl, 5-hydroxypentyl or the like.

The term "cyano-C₁₋₆alkyl" means a substituted C₁₋₆alkyl group having cyano group, such as cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, 4-cyanobutyl, 5-cyanopentyl or the like.

The term "carbamoyl-C₁₋₆alkyl" means a substituted C₁₋₆alkyl group having 15 a carbamoyl group, such as carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl, 3-carbamoylpropyl, 4-carbamoylbutyl, 5-carbamoylpentyl or the like.

The term "di(C₁₋₆alkyl)amino" means an amino group having two above-mentioned C₁₋₆alkyl groups, such as dimethylamino, diethylamino, dipropylamino or the like.

20 The term "di(C₁₋₆alkyl)amino-C₁₋₆alkyl" means a substituted C₁₋₆alkyl group having the above-mentioned di(C₁₋₆alkyl)amino group, such as 2-dimethylaminoethyl, 3-dimethylaminopropyl or the like.

The term "aryl" means a monocyclic or bicyclic group of 6 to 12 ring carbon atoms having at least one aromatic ring, such as phenyl, naphthyl, or the like.

25 The term "aryl-C₁₋₆alkyl" means a substituted C₁₋₆alkyl group having an above-mentioned aryl group, such as benzyl, phenethyl or the like.

The term "heteroaryl" means a monocyclic or bicyclic group of 5 to 12 ring atoms having at least one aromatic ring having in its ring 1 to 4 atoms which may be the same or different and are selected from nitrogen, oxygen and sulfur, such as 30 pyridyl, pyrimidinyl, imidazolyl, quinolyl, indolyl, benzofuranyl, quinoxaliny, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl or the like.

The term "halogen" means fluorine, chlorine, bromine or iodine atom.

The term "C₂₋₆alkenyl" means a straight chain or branched chain alkenyl

group of 2 to 6 carbon atoms, such as vinyl, isopropenyl, allyl or the like.

The term "C₂₋₆alkynyl" means a straight chain or branched chain alkynyl group of 2 to 6 carbon atoms, such as ethynyl, prop-1-ynyl, prop-2-ynyl or the like.

The term "C₁₋₆alkylthio" means a straight chain or branched chain alkylthio group of 1 to 6 carbon atoms, such as methylthio, ethylthio, propylthio or the like.

The term "C₁₋₆alkylsulfinyl" means a straight chain or branched chain alkylsulfinyl group of 1 to 6 carbon atoms, such as methylsulfinyl, ethylsulfinyl, propylsulfinyl or the like.

The term "C₁₋₆alkylsulfonyl" means a straight chain or branched chain alkylsulfonyl group of 1 to 6 carbon atoms, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl or the like.

The phrase "aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkylthio, C₁₋₆alkylsulfinyl, C₁₋₆alkylsulfonyl, cyano, nitro, hydroxy, -CO₂R⁸, -C(=O)R⁹, -CONR¹⁰R¹¹, -OC(=O)R¹², -NR¹³CO₂R¹⁴, -S(=O)_rNR¹⁵R¹⁶, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy and -N(R¹⁷)R¹⁸" includes, for example, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 2,4-dibromophenyl, 2-bromo-4-isopropylphenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2-chloro-4-trifluoromethylphenyl, 4-methoxy-2-methylphenyl, 2-chloro-4-trifluoromethoxyphenyl, 4-isopropyl-2-methylthiophenyl, 2,4,6-trimethylphenyl, 4-bromo-2,6-dimethylphenyl, 4-bromo-2,6-diethylphenyl, 4-chloro-2,6-dimethylphenyl, 2,4,6-tribromophenyl, 2,4,5-tribromophenyl, 2,4,6-trichlorophenyl, 2,4,5-trichlorophenyl, 4-bromo-2,6-dichlorophenyl, 6-chloro-2,4-dibromophenyl, 2,4-dibromo-6-fluorophenyl, 2,4-dibromo-6-methylphenyl, 2,4-dibromo-6-methoxyphenyl, 2,4-dibromo-6-methylthiophenyl, 2,6-dibromo-4-isopropylphenyl, 2,6-dibromo-4-trifluoromethylphenyl, 2-bromo-4-trifluoromethylphenyl, 4-bromo-2-chlorophenyl, 2-bromo-4-chlorophenyl, 4-bromo-2-methylphenyl, 4-chloro-2-methylphenyl, 2,4-dimethoxyphenyl, 2,6-dimethyl-4-methoxyphenyl, 4-chloro-2,6-dibromophenyl, 4-bromo-2,6-difluorophenyl, 2,6-dichloro-4-trifluoromethylphenyl, 2,6-dichloro-4-trifluoromethoxyphenyl, 2,6-dibromo-4-trifluoromethoxyphenyl, 2-chloro-4,6-dimethylphenyl, 2-bromo-4,6-dimethoxyphenyl, 2-bromo-4-isopropyl-6-methoxyphenyl, 2,4-dimethoxy-6-

methylphenyl, 6-dimethylamino-4-methylpyridin-3-yl, 2-chloro-6-trifluoromethylpyridin-3-yl, 2-chloro-6-trifluoromethoxypyridin-3-yl, 2-chloro-6-methoxypyridin-3-yl, 6-methoxy-2-trifluoromethylpyridin-3-yl, 2-chloro-6-difluoromethylpyridin-3-yl, 6-methoxy-2-methylpyridin-3-yl, 2,6-dimethoxypyridin-3-yl, 4,6-dimethyl-2-trifluoromethylpyrimidin-5-yl, 2-dimethylamino-6-methylpyridin-3-yl.

The “pharmaceutically acceptable salts” in the present invention include, for example, salts with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid or the like; salts with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, camphorsulfonic acid, ethanesulfonic acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, malic acid, malonic acid, mandelic acid, galactaric acid, naphthalene-2-sulfonic acid or the like; salts with one or more metal ions such as lithium ion, sodium ion, potassium ion, calcium ion, magnesium ion, zinc ion, aluminium ion or the like; salts with amines such as ammonia, arginine, lysine, piperazine, choline, diethylamine, 4-phenylcyclohexylamine, 2-aminoethanol, benzathine or the like.

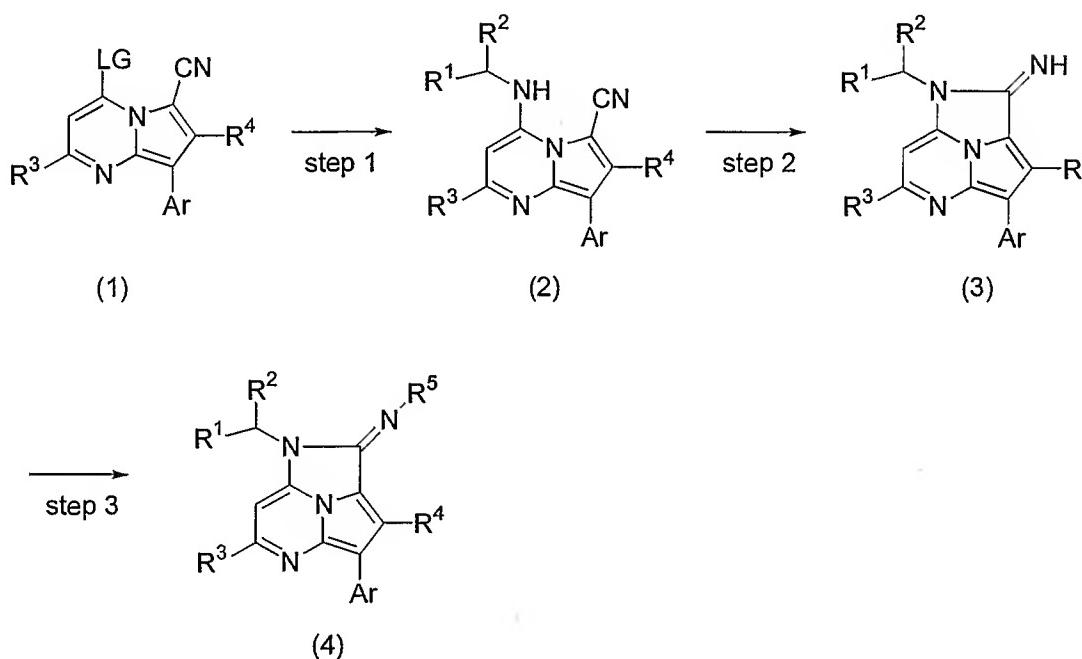
In a compound of the present invention, isomers such as diastereomers, enantiomers, geometric isomers and tautomeric forms may exist. The compound of the present invention includes any individual isomers and the racemic and non-racemic mixtures of the isomers.

Preferable examples of the compound of the present invention are as follows.

That is preferable are compounds represented by the formula [I], wherein R³ is C₁₋₆alkyl; R⁴ is hydrogen or C₁₋₆alkyl; R⁵ is hydrogen or C₁₋₆alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C₁₋₃alkyl, C₁₋₃alkoxy, C₁₋₃alkylthio, trifluoromethyl, trifluoromethoxy and -N(R¹⁷)R¹⁸ (wherein R¹⁷ and R¹⁸ are the same or different, and independently are hydrogen or C₁₋₃alkyl). More preferable are compounds of formula [I], wherein R³ is C₁₋₃alkyl; R⁴ is hydrogen or C₁₋₆alkyl; R⁵ is hydrogen or C₁₋₃alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen or C₁₋₃alkyl.

The compound of the formula [I] can be produced, for example, by the process shown in the following reaction scheme 1 (in the following reaction scheme, R¹, R², R³, R⁴ and Ar are as defined above, LG is chloro, bromo, iodo, methanesulfonyloxy, benzenesulfonyloxy, toluenesulfonyloxy, 5 trifluoromethanesulfonyloxy group, R^a-S(O)- or R^a-S(O)₂-, wherein R^a is C₁₋₆alkyl or benzyl).

Reaction Scheme 1



Step 1:

- Compound (2) can be obtained by reacting Compound (1) with the 10 corresponding amine in an inert solvent in the presence or absence of a base. Herein, the base includes, for example, amines such as triethylamine, N,N-diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, potassium hydroxide, sodium hydroxide, lithium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for 15

- example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dichloromethane; chloroform; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

Step 2:

- Conversion of Compound (2) into Compound (3) can be achieved in the presence of an acid in an inert solvent. Herein, the acid is an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid or the like; an organic acid such as acetic acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, camphorsulfonic acid, trifluoroacetic acid, trifluoromethanesulfonic acid or the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dichloromethane; chloroform; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

Step 3:

- Conversion of Compound (3) into Compound (4) can be achieved by using an alkylating reagent in the presence or absence of a base in an inert solvent (when R⁵ is C₁₋₆alkyl) or reacting with a carbonylating reagent in the presence or absence of a base in an inert solvent and then treatment of ammonia (when R⁵ is carbamoyl). Herein, the alkylating reagent includes conventional alkylating reagents such as iodomethane, iodoethane, bromomethane, bromoethane, dimethylsulfate, diethylsulfate or the like. The carbonylating reagent includes conventional carbonylating reagents such as phosgene, diphosgene, triphosgene, 1,1'-carbonyldiimidazole or the like. The base includes, for example, amines such as triethylamine, *N,N*-diisopropylethylamine, pyridine and the like; inorganic bases

such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, potassium hydroxide, sodium hydroxide, lithium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dichloromethane; chloroform; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

The compound of the present invention can be converted to a salt with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid or the like; with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, camphorsulfonic acid, ethanesulfonic acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, malic acid, malonic acid, mandelic acid, galactaric acid, naphthalene-2-sulfonic acid or the like; with an inorganic base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, aluminium hydroxide or the like; or with an organic base such as ammonia, arginine, lysine, piperazine, choline, diethylamine, 4-phenylcyclohexylamine, 2-aminoethanol, benzathine or the like in an inert solvent.

The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; esters such as ethyl acetate, ethyl formate and the like; ketones such as acetone, methyl ethyl ketone and the like; hydrocarbons such as benzene, toluene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dichloromethane; chloroform; dimethyl sulfoxide; pyridine; water; and

10

mixtures of solvents selected from these inert solvents.

The compound of the present invention is useful as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved. For this purpose, the compound of the present invention can be formulated into tablets, pills, capsules, granules, powders, solutions, emulsions, suspensions, injections and the like by a conventional preparation technique by adding conventional fillers, binders, disintegrators, pH-adjusting agents, solvents, etc.

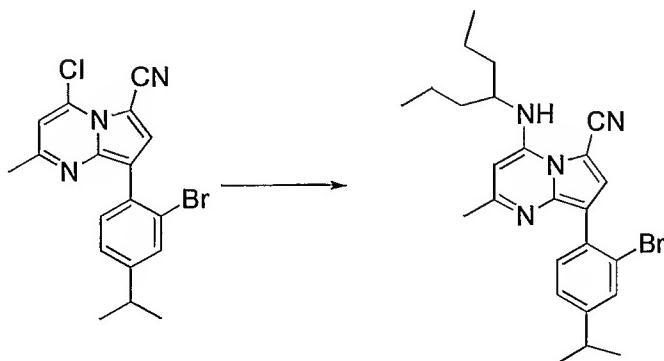
The compound of the present invention can be administered to an adult patient in a dose of 0.1 to 500 mg per day in one portion or several portions orally or 10 parenterally. The dose can be properly increased or decreased depending on the kind of a disease and the age, body weight and symptom of a patient.

ENBODIMENTS OF THE INVENTION

The present invention is concretely explained with reference to the following examples and test example, but is not limited thereto.

15 Example 1

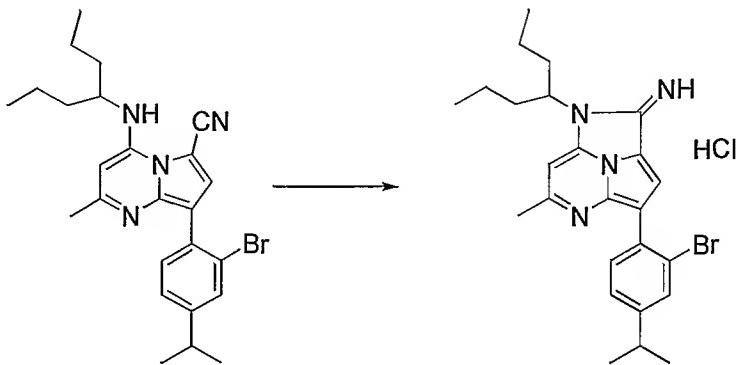
Synthesis of [4-(2-bromo-4-isopropyl-phenyl)-6-methyl-1-(1-propyl-butyl)-
1*H*-1,5,7*b*-triaza-cyclopenta[*cd*]inden-2-ylidene]-methyl-amine hydrochloride
(compound 1-010)



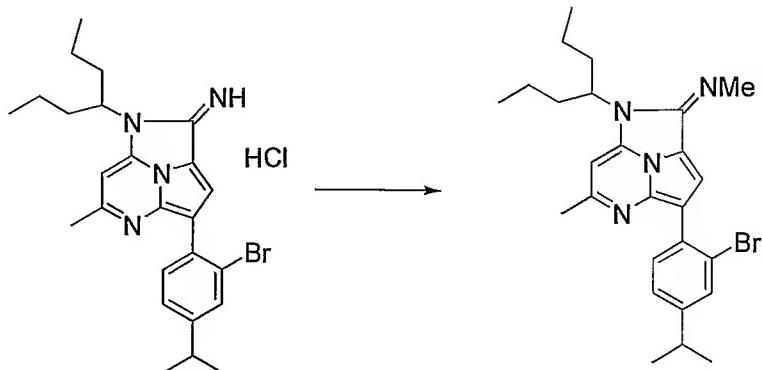
(1) A mixture of 8-(2-bromo-4-isopropyl-phenyl)-4-chloro-2-methyl-
20 pyrrolo[1,2-*a*]pyrimidine-6-carbonitrile (300 mg), 1-propyl-butylamine (267 mg),
N,N-diisopropylethylamine (300 mg) in ethanol (1.0 mL) was heated at reflux
overnight. The reaction mixture was cooled to room temperature, poured into a
saturated aqueous sodium hydrogencarbonate, and then extracted with chloroform.
The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate

11

was concentrated under reduced pressure and purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: hexane / ethyl acetate = 20 : 1) to give 8-(2-bromo-4-isopropyl-phenyl)-2-methyl-4-(1-propyl-butylamino)-pyrrolo[1,2-*a*]pyrimidine-6-carbonitrile (321 mg) as a pale brown solid.



- 5 (2) To a suspension of 8-(2-bromo-4-isopropyl-phenyl)-2-methyl-4-(1-propyl-butylamino)-pyrrolo[1,2-*a*]pyrimidine-6-carbonitrile (321 mg) in ethanol (1.5 mL) was added conc. HCl (0.75 mL) and heated for 50 °C for 3 hours. The reaction mixture was cooled to room temperature, poured into a saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give crude product. To a solution of the crude product in ethyl acetate (2 mL) and ethanol (0.2 mL) was added 4M HCl / ethyl acetate (0.25 mL) under ice-cooling and concentrated under reduced pressure. The residue was crystallized from ethyl acetate to provide 4-(2-bromo-4-isopropyl-phenyl)-6-methyl-1-(1-propyl-butyl)-1*H*-1,5,7*b*-triaza-cyclopenta[*cd*]inden-2-ylideneamine hydrochloride (350 mg) as a solid.
- 10
- 15



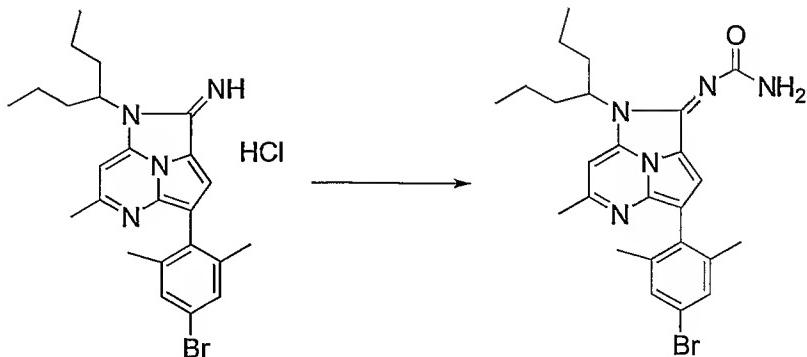
(3) To a mixture of 4-(2-bromo-4-isopropyl-phenyl)-6-methyl-1-(1-propyl-butyl)-1*H*-1,5,7*b*-triaza-cyclopenta[*cd*]inden-2-ylideneamine hydrochloride (350 mg) and dimethylsulfate (866 mg) in tetrahydrofuran (3.5 mL) was added NaH (60% in oil, 139 mg) and heated at 65 °C for 1 hour. After addition of water, the reaction mixture was poured into 2.5 M NaOH aqueous solution, extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by a silica gel column chromatography (silica gel: Wako Gel (C200), eluent: chloroform / ethyl acetate = 10 : 1) to give [4-(2-bromo-4-isopropyl-phenyl)-6-methyl-1-(1-propyl-butyl)-1*H*-1,5,7*b*-triaza-cyclopenta[*cd*]inden-2-ylidene]-methyl-amine (135 mg)

(4) To a suspension of [4-(2-bromo-4-isopropyl-phenyl)-6-methyl-1-(1-propyl-butyl)-1*H*-1,5,7*b*-triaza-cyclopenta[*cd*]inden-2-ylidene]-methyl-amine (135 mg) in a mixture of ethyl acetate (1.5 mL) and ethanol (0.2 mL) was added 4M HCl / ethyl acetate (0.25 mL) and concentrated under reduced pressure. The residue was solidified from Et₂O to provide the title compound as an amorphous (73 mg).

Table 1 lists the compound obtained in Example 1 and compounds obtained by the similar procedure as described in Example 1.

Example 2

Synthesis of [4-(4-bromo-2,6-dimethyl-phenyl)-6-methyl-1-(1-propyl-butyl)-1*H*-1,5,7*b*-triaza-cyclopenta[*cd*]inden-2-ylidene]-urea (compound 1-013)



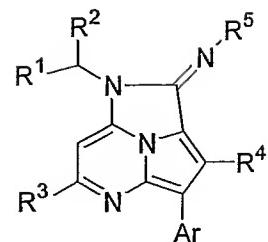
To a solution of triphosgene (1.82 g) in chloroform (9 mL) was added dropwise a

13

solution of 4-(4-bromo-2,6-dimethyl-phenyl)-6-methyl-1-(1-propyl-butyl)-1*H*-
1,5,7*b*-triaza-cyclopenta[*cd*]inden-2-ylideneamine hydrochloride (300 mg)
synthesized by the same procedure as in example 1 and *N,N*-diisopropylethylamine
(174 mg) in chloroform (3 mL) in an ice-cooling bath and stirred at room
5 temperature for 1 hour. The reaction mixture was added dropwise into 25 % an
aqueous NH₃ solution (10 mL) in an ice-cooling bath and stirred at room
temperature for 2 hours. The reaction mixture was poured into H₂O and extracted
with chloroform. The organic layer was washed with brine, dried over anhydrous
sodium sulfate and filtered. The filtrate was concentrated under reduced pressure
10 and the residue was purified by a silica gel column chromatography (silica gel:
Wako Gel (C200), eluent: hexane / ethyl acetate = 1 : 1) to give a solid. The solid
was washed with diisopropylether and the title compound (42 mg) was obtained.

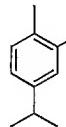
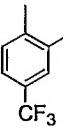
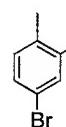
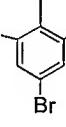
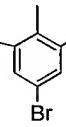
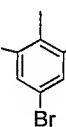
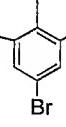
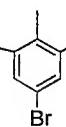
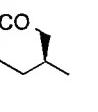
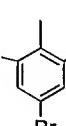
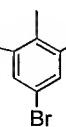
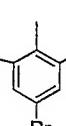
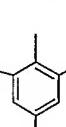
Table 1^{*1}

14



Com. No.	Ex. No.	R^2 	R^3	R^4	R^5	Ar 	melting point (°C) (solvent for crystallization)
1-001	1		CH ₃	H	H		202-204 ^{*2} (EtOAc / IPE)
1-002	1		CH ₃	H	H		204-206 ^{*2} (EtOAc / IPE)
1-003	1		CH ₃	H	H		206-208 ^{*2} (EtOAc / IPE)
1-004	1		CH ₃	H	H		201-203 ^{*2} (H ₂ O)
1-005	1		CH ₃	H	H		amorphous ^{*2}
1-006	1		CH ₃	H	H		218-220 ^{*2} (H ₂ O)
1-007	1		CH ₃	H	H		220-222 ^{*2} (H ₂ O)
1-008	1		CH ₃	H	CH ₃		183-185 ^{*3} (EtOAc)
1-009	1		CH ₃	H	CH ₃		192-194 ^{*3} (EtOAc)

15

1-010	1		CH ₃	H	CH ₃		amorphous ^{*2}
1-011	1		CH ₃	H	CH ₃		amorphous ^{*2}
1-012	1		CH ₃	H	CH ₃		amorphous ^{*2}
1-013	2		CH ₃	H	CONH ₂		198-200 (IPE)
1-014	1		CH ₃	H	H		214-216 (H ₂ O)
1-015	1		CH ₃	H	CH ₃		180-182 ^{*3} (EtOAc)
1-016	1		CH ₃	H	H		amorphous ^{*2}
1-017	1		CH ₃	H	CH ₃		185-187 ^{*3} (EtOAc)
1-018	1		CH ₃	H	H		amorphous ^{*2}
1-019	1		CH ₃	H	CH ₃		188-190 ^{*3} (EtOAc)
1-020	1		CH ₃	H	H		amorphous ^{*2}
1-021	1		CH ₃	H	CH ₃		174-176 ^{*3} (EtOAc)

16

1-022	1		CH ₃	H	H		amorphous ^{*2}
-------	---	--	-----------------	---	---	--	-------------------------

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization; EtOAc = ethyl acetate, IPE = diisopropylether

Analytical data of non-crystal compounds are described below.

1-005:

5 MS (Pos, ES): 467 ($M + 1$)⁺, 469 ($M + 3$)⁺, 489 ($M + Na$)⁺, 491 ($M + Na + 2$)⁺; NMR (300 MHz, CDCl₃) δ 0.95 (6 H, t, *J* = 7.3 Hz), 1.29 (6 H, t, *J* = 7.0 Hz), 1.12-1.40 (2 H, m), 1.43-1.73 (2 H, m), 1.92-2.15 (4 H, m), 2.82-3.00 (1 H, m), 2.91 (3 H, s), 5.48 (1 H, br s), 7.10 (1 H, s), 7.22-7.30 (1 H, m), 7.55-7.63 (2 H, m), 8.57 (1 H, s), 11.10 (1 H, br s)

10 1-010:

MS (Pos, ES): 481 ($M + 1$)⁺, 483 ($M + 3$)⁺; NMR (300 MHz, CDCl₃) δ 0.94 (6 H, t, *J* = 7.3 Hz), 1.18-1.40 (2 H, m), 1.31 (6 H, d, *J* = 6.8 Hz), 1.44-1.80 (2 H, m), 1.91-2.20 (4 H, m), 2.88-3.04 (1 H, m), 2.94 (3 H, s), 3.48 (3 H, d, *J* = 4.2 Hz), 5.81 (1 H, br s), 7.17 (1 H, s), 7.34 (1 H, dd, *J* = 1.7, 7.9 Hz), 7.63 (1 H, d, *J* = 1.7 Hz), 7.74 (1 H, d, *J* = 7.9 Hz), 8.04 (1 H, s), 12.5 (1 H, br s)

15 1-011:

MS (Pos, ES): 507 ($M + 1$)⁺, 509 ($M + 3$)⁺; NMR (300 MHz, CDCl₃) δ 0.95 (6 H, t, *J* = 7.3 Hz), 1.19-1.40 (2 H, m), 1.46-1.80 (2 H, m), 1.91-2.20 (4 H, m), 2.95 (3 H, s), 3.50 (3 H, d, *J* = 4.7 Hz), 5.86 (1 H, br s), 7.20 (1 H, s), 7.75 (1 H, d, *J* = 8.0 Hz), 8.02 (1 H, d, *J* = 8.0 Hz), 8.05 (1 H, s), 8.15 (1 H, s), 12.85 (1 H, br s)

20 1-012:

MS (Pos, ES): 517 ($M + 1$)⁺, 519 ($M + 3$)⁺, 521 ($M + 5$)⁺; NMR (300 MHz, CDCl₃) δ 0.94 (6 H, t, *J* = 7.2 Hz), 1.16-1.38 (2 H, m), 1.42-1.80 (2 H, m), 1.88-2.20 (4 H, m), 2.94 (3 H, s), 3.49 (3 H, d, *J* = 4.2 Hz), 5.83 (1 H, br s), 7.18 (1 H, s), 7.62 (1 H, dd, *J* = 1.9, 8.3 Hz), 7.74 (1 H, d, *J* = 8.3 Hz), 7.95 (1 H, d, *J* = 1.9 Hz), 8.08 (1 H, s), 12.72 (1 H, br s)

17

1-016:

MS (Pos, ES): 441 ($M + 1$)⁺, 443 ($M + 3$)⁺; NMR (200 MHz, CDCl₃) δ 1.10 (3 H, t, *J* = 7.5 Hz), 1.85-2.38 (9 H, m), 2.84 (3 H, s), 3.42 (3 H, s), 3.89-4.10 (2 H, m), 5.38-5.51 (1 H, br s), 7.30-7.34 (3 H, m), 8.22 (1 H, s), 10.70-10.86 (1 H, br s)

5 1-018:

MS (Pos, ES): 441 ($M + 1$)⁺, 443 ($M + 3$)⁺; NMR (300 MHz, CDCl₃) δ 1.10 (3 H, t, *J* = 7.5 Hz), 1.90-2.35 (9 H, m), 2.84 (3 H, s), 3.42 (3 H, s), 3.90-4.08 (2 H, m), 5.40-5.50 (1 H, br s), 7.22-7.40 (3 H, m), 8.22 (1 H, s), 10.75-10.90 (1 H, br s)

1-020:

10 MS (Pos, ES): 439 ($M + 1$)⁺, 441 ($M + 3$)⁺; NMR (300 MHz, CDCl₃) δ 1.01 (3 H, d, *J* = 6.6 Hz), 1.09 (3 H, d, *J* = 6.6 Hz), 1.52-2.03 (6 H, m), 2.03-2.20 (7 H, m), 2.87 (3 H, s), 5.45-5.58 (1 H, m), 7.15 (1 H, s), 7.31 (2 H, s), 8.25 (1 H, s), 10.90-11.10 (1 H, m)

1-022:

15 MS (Pos, ES): 457 ($M + 1$)⁺, 459 ($M + 3$)⁺; NMR (300 MHz, CDCl₃) δ 2.11 (6 H, s), 2.85 (3 H, s), 3.40 (6 H, s), 3.94-4.03 (2 H, m), 4.16-4.27 (2 H, m), 5.68 (1 H, br s), 7.28 (1 H, s), 7.32 (2 H, s), 8.20 (1 H, s)

*2: HCl salt

*3: 2 PhSO₃H salt

20

Test Example [CRF receptor binding test]

Monkey amygdala membranes were used as a receptor preparation.

¹²⁵I-CRF was used as ¹²⁵I-labeled ligand.

Binding reaction using the ¹²⁵I-labeled ligand was carried out by the
25 following method described in The Journal of Neuroscience, 7, 88 (1987).

Preparation of receptor membranes:

Monkey amygdala was homogenized in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM MgCl₂, 2 mM EDTA and centrifuged at 48,000 × g for 20 min, and the precipitate was washed once with Tris-HCl buffer. The washed precipitate

was suspended in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM MgCl₂, 2 mM EDTA, 0.1% bovine serum albumin and 100 kallikrein units/ml aprotinin, to obtain a membrane preparation.

CRF receptor binding test:

5 The membrane preparation (0.3 mg protein/ml), ¹²⁵I-CRF (0.2 nM) and a test drug were reacted at 25°C for 2 hours. After completion of the reaction, the reaction mixture was filtered by suction through a glass filter (GF/C) treated with 0.3% polyethylene imine, and the glass filter was washed three times with phosphate-buffered saline containing 0.01% Triton X-100. After the washing, the
10 radioactivity of the filter paper was measured in a gamma counter.

The amount of ¹²⁵I-CRF bound when the reaction was carried out in the presence of 1 μM CRF was taken as the degree of nonspecific binding of ¹²⁵I-CRF, and the difference between the total degree of ¹²⁵I-CRF binding and the degree of nonspecific ¹²⁵I-CRF binding was taken as the degree of specific ¹²⁵I-CRF binding.

15 An inhibition curve was obtained by reacting a definite concentration (0.2 nM) of ¹²⁵I-CRF with various concentrations of each test drug under the conditions described above. A concentration of the test drug at which binding of ¹²⁵I-CRF is inhibited by 50% (IC₅₀) was determined from the inhibition curve.

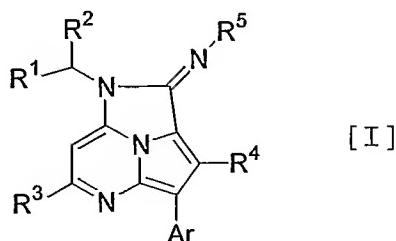
As a result, it was found that compounds 1-001, 1-002, 1-003, 1-008, 1-009,
20 1-015, 1-017 and 1-021 can be exemplified as typical compounds having an IC₅₀ value of 100 nM or less.

EFFECT OF THE INVENTION

According to the present invention, compounds having a high affinity for CRF receptors have been provided. These compounds are effective against
25 diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastral diseases, drug dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alpecia, irritable bowel syndrome, sleep disorders,
30 dermatitides, schizophrenia, pain, etc.

CLAIMS

1. A triaza-cyclopenta[cd]indene derivative represented by the following formula [I]:



(wherein R¹ and R² are the same or different, and independently are hydrogen, C₁-alkyl, C₃-₇cycloalkyl, C₃-₇cycloalkyl-C₁-alkyl, C₁-alkoxy-C₁-alkyl, hydroxy-C₁-alkyl, cyano-C₁-alkyl, carbamoyl-C₁-alkyl or di(C₁-alkyl)amino-C₁-alkyl, cyano, carbamoyl or aryl;

R³ is hydrogen, C₁-alkyl, C₃-₇cycloalkyl, C₃-₇cycloalkyl-C₁-alkyl, halogen, C₁-alkoxy, C₃-₇cycloalkyloxy, C₁-alkylthio or -N(R⁶)R⁷;

R⁴ is hydrogen, C₁-alkyl, C₃-₇cycloalkyl or C₃-₇cycloalkyl-C₁-alkyl;

R⁵ is hydrogen, C₁-alkyl, aryl-C₁-alkyl or carbamoyl;

Ar is aryl or heteroaryl which aryl or heteroaryl is unsubstituted or substituted with 1 or more substituents, which are the same or different, selected from the group consisting of halogen, C₁-alkyl, C₃-₇cycloalkyl, C₂-alkenyl, C₂-alkynyl, C₁-alkoxy, C₁-alkylthio, C₁-alkylsulfinyl, C₁-alkylsulfonyl, cyano, nitro, hydroxy, -CO₂R⁸, -C(=O)R⁹, -CONR¹⁰R¹¹, -OC(=O)R¹², -NR¹³CO₂R¹⁴, -S(=O)_rNR¹⁵R¹⁶, trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoromethoxy and -N(R¹⁷)R¹⁸;

R⁸ and R¹⁴ are the same or different, and independently are hydrogen or C₁-alkyl, C₃-₈cycloalkyl, C₃-₈cycloalkyl-C₁-alkyl, aryl or aryl-C₁-alkyl;

R⁶, R⁷, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are the same or different, and independently are hydrogen, C₁-alkyl or C₃-₇cycloalkyl;

r is 1 or 2) or individual isomers thereof or racemic or non-racemic mixtures of isomers thereof, or pharmaceutically acceptable salts and hydrates thereof.

2. The triaza-cyclopenta[cd]indene derivative according to claim 1 represented by the formula [I], wherein R³ is C₁-alkyl; R⁴ is hydrogen or C₁-alkyl;

20

R^5 is hydrogen or C_{1-6} alkyl; Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, trifluoromethyl, trifluoromethoxy and $-N(R^{17})R^{18}$ (wherein R^{17} and R^{18} are the same or different, and independently are hydrogen or C_{1-3} alkyl); R^1 , R^2 and R^4 are as defined in claim 1, or pharmaceutically acceptable salts and hydrates thereof.

3. The triaza-cyclopenta[cd]indene derivative according to claim 1 represented by the formula [I], wherein R^3 is C_{1-3} alkyl; R^5 is hydrogen or C_{1-3} alkyl;

Ar is phenyl which phenyl is substituted with two or three substituents, which are the same or different, selected from the group consisting of halogen and C_{1-3} alkyl; R^1 , R^2 and R^4 are as defined in claim 1, or pharmaceutically acceptable salts and hydrates thereof.

4. An antagonist for CRF receptors, comprising a triaza-cyclopenta[cd]indene derivative, a pharmaceutically acceptable salt thereof or its hydrate according to any one of claims 1 to 3, as an active ingredient.

5. Use of a triaza-cyclopenta[cd]indene derivative, a pharmaceutically acceptable salt thereof or its hydrate according to any one of claim 1 to 3, for the manufacture of a therapeutic agent as an antagonist for CRF receptors.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2005/000323

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D487/16 A61K31/505 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/83486 A (DUPONT PHARMACEUTICALS COMPANY) 8 November 2001 (2001-11-08) the whole document -----	1-5
A	WO 02/094826 A (NEUROCRINE INC; SB PHARMCO PUERTO RICO INC; DI FABIO, ROMANO; GENTILE,) 28 November 2002 (2002-11-28) the whole document -----	1-5
A	WO 01/87889 A (NEUROCRINE BIOSCIENCES, INC; HADDACH, MUSTAPHA) 22 November 2001 (2001-11-22) the whole document -----	1-5



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

29 April 2005

Date of mailing of the international search report

09/05/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP2005/000323

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0183486	A	08-11-2001	AU CA EP JP WO US	5567301 A 2407597 A1 1278751 A1 2003531909 T 0183486 A1 2002022619 A1		12-11-2001 08-11-2001 29-01-2003 28-10-2003 08-11-2001 21-02-2002
WO 02094826	A	28-11-2002	BR CA CN CZ EP WO HU JP NZ US	0209947 A 2450535 A1 1529705 A 20033165 A3 1392689 A1 02094826 A1 0400854 A2 2004530702 T 529471 A 2004198726 A1		27-04-2004 28-11-2002 15-09-2004 13-10-2004 03-03-2004 28-11-2002 30-08-2004 07-10-2004 19-12-2003 07-10-2004
WO 0187889	A	22-11-2001	AT AU DE DE EP ES JP WO US US	260918 T 6332901 A 60102231 D1 60102231 T2 1282624 A1 2214422 T3 2003533527 T 0187889 A1 2004014747 A1 2002032194 A1		15-03-2004 26-11-2001 08-04-2004 14-04-2005 12-02-2003 16-09-2004 11-11-2003 22-11-2001 22-01-2004 14-03-2002